IFW

PATENT
Attorney Docket No. **056291-5256**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Margaretha Grind**	)	
	)	
Application No. **10/550,154**	)	Group Art Unit: **1614**
	)	
Filed: **September 20, 2005**	)	Examiner: **Not Assigned**
	)	
For: **Use of Low Molecular Weight Thrombin Inhibitors in Cholesterol-Lowering Therapy**	)	

SUBMISSION OF PRIORITY DOCUMENT

Under the provisions of 35 U.S.C. § 119, Applicant hereby claims the benefit of the filing date of UK Patent Application No. 0306615.6 filed March 22, 2003 for the above-identified U.S. Patent Application.

In support of Applicant's claim for priority, filed herewith is one certified copy of the above.

Respectfully submitted,

Morgan, Lewis & Bockius LLP

Dated: **July 11, 2006**
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PCT / SE 2004 / 000417

INVESTOR IN PEOPLE

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Signed R. Mahoney

Dated 20 February 2004

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

1.	Your reference	ASTZ / P28053GB
2.	Patent application number *(The Patent Office will fill in this part)*	0306615.6 22 MAR 2003
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	**AstraZeneca AB** S-151 85 Södertälje Sweden 24MAR03 E774411-1 002866 P01/7700 0.00-0306615.6
	Patents ADP number *(if you know it)*	7822448003
	If the applicant is a corporate body, give the country/state of its incorporation	Sweden
4.	Title of the invention	NEW USE
5.	Name of your agent *(if you have one)*	**ERIC POTTER CLARKSON** **PARK VIEW HOUSE** **58 THE ROPEWALK** **NOTTINGHAM** **NG1 5DD**
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	
	Patents ADP number *(if you know it)*	**1305010**

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* YES

a) *any applicant named in part 3 is not an inventor; or*
b) *there is an inventor who is not named as an applicant, or*
c) *any named applicant is a corporate body. See note (d))*

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	20
Claims(s)	8
Abstract	1
Drawing(s)	2+2

10. If you are also filing in any of the following, state how many against each item.

Priority Documents	0
Translations of priority documents	0
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	NO
Request for preliminary examination and search *(Patents Form 9/77)*	YES
Request for substantive examination *(Patents Form 10/77)*	NO
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Eric Potter Clarkson Date
ERIC POTTER CLARKSON 21 March 2003

12. Name and daytime telephone number of person to contact in the United Kingdom **0115 9552211**

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After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 01645 500505.
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NEW USE

Field of the Invention

This invention relates to a new use of low molecular weight thrombin inhibitors.

Background and Prior Art

It is well known that high levels of cholesterol are associated with heart disease. More than half of all US citizens are understood to have cholesterol levels that exceed those recommended, and one in five has cholesterol levels that are considered high.

Cholesterol is involved in the production and maintenance of cell membranes, as well as the production of sex hormones (including progesterone, testosterone, estradiol and cortisol), bile salts and Vitamin D. It is formed primarily in the liver, but also in other parts of the body, such as the small intestine.

In healthy individuals, all of the cholesterol that is needed to perform the above-mentioned functions is produced naturally. However, in a typical blood test, of the amount of cholesterol circulating in blood, about 85% is endogenous, the other 15% arising from external sources. Dietary cholesterol usually originates from meat, poultry, fish, seafood and dairy products. In this respect, high consumption levels of these foodstuffs may give rise to increased cholesterol levels in the bloodstream.

Increased cholesterol levels in serum have been associated with atherosclerosis, which is known to increase significantly the risk of blood vessel blockage (stenosis), and thus the likelihood of angina pectoris, myocardial infarction and other cardiovascular complications, such as stroke.

Cholesterol is insoluble in aqueous environments and thus needs to be transported within the bloodstream by apolipoproteins (Apos). When apolipoproteins are associated with cholesterol, complexes known as lipoproteins are formed. The density of these lipoproteins is determined by the amount of protein in the molecule and, in this respect, low-density lipoproteins (LDLs), which are the major cholesterol carrier in the blood, are known to have more of the negative effects mentioned herein than protective high-density lipoproteins (HDLs). High levels of LDLs are thus associated with atherosclerosis, whereas greater levels of HDLs are understood to provide some protection against stenosis, and hence coronary risk, by way of removal of excess cholesterol (transporting it to the liver for disposal).

A third group of carrier molecules, very low-density lipoproteins (VLDLs) are converted to LDLs following the delivery of triglycerides to the muscles and adipose tissue. Triglycerides are a mixture of fatty acids and glycerol and are the major components of lipids circulating in blood. Like cholesterol, triglycerides are substances that are found endogenously in the bloodstream, and may be deposited in adipose tissue. Triglycerides contain high-energy fatty acids which provide much of the fuel needed for normal cellular function. However, an excessive amount of triglycerides, or VLDLs, in the bloodstream can result in similar problems to those

associated with high cholesterol and LDL levels, as well as obesity and diabetes.

Thus, levels of HDLs, LDLs, total cholesterol and triglycerides are all key indicators in determining the risk of atherosclerosis and associated cardiovascular disorders, such as coronary artery diseases (e.g. angina pectoris, myocardial infarction, etc.), stroke (including cerebro-vascular accident and transient ischaemic attack), peripheral arterial occlusive disease, obesity and diabetes. Patients with high overall cholesterol and/or triglycerides levels are at a significant risk, irrespective of whether or not they also have a favourable HDL level. Patients with normal cholesterol levels but low HDL levels are also at increased risk. Recently, it has also been noted that the level of risk of cardiovascular disease associated with high levels of apolipoprotein B (ApoB; which carries lipids in VLDLs and LDLs), and/or low levels of apolipoprotein A-I (ApoA-I; which carries lipids in HDLs), is extremely high.

There are numerous factors that influence cholesterol and triglyceride levels, including diet, age, weight, gender, genetics, diseases (such as diabetes) and lifestyle.

Positive changes in relation to diet, lifestyle and exercise are often insufficient to decrease the risk of cardiovascular problems. In such instances, cholesterol- and/or triglyceride-lowering medication may be prescribed.

Drugs that reduce LDL levels in serum can prevent or reduce the build-up of artery blocking plaques, and can reduce the risk of plaque rupture and associated thrombo-embolic complications. There are several types of drugs

that can help reduce blood cholesterol levels. The most commonly prescribed are the statins, HMG-CoA reductase inhibitors, such as lovastatin, pravastatin, fluvastatin, simvastatin, atorvastatin and rosuvastatin. These drugs prevent directly the formation of cholesterol in the liver and thus reduce the risk of cardiovascular disease. Other prescribed drug categories include resins (such as cholestyramine and colestipol), which act by binding bile acids, so causing the liver to produce more of the latter, and using up cholesterol in the process. Further, the B vitamin niacin has been reported at high doses to lower triglycerides and LDL levels in addition to increasing HDL levels. Fibrates (such as gemfibrozil and fenofibrate) are known to lower triglycerides and can increase HDL levels.

However, some of these drugs are known to have side effects, including liver damage. Hence, there is a need for alternative and/or more effective drugs for use in cholesterol-lowering therapy.

The early development of low molecular weight inhibitors of thrombin has been described by Claesson in Blood Coagul. Fibrinol. (1994) 5, 411. Low molecular weight thrombin inhibitors (and prodrugs thereof) have been described more recently in US Patent N° 4,346,078; International Patent Applications WO 93/11152, WO 93/18060, WO 93/05069, WO 94/20467, WO 94/29336, WO 95/35309, WO 95/23609, WO 96/03374, WO 96/06832, WO 96/06849, WO 96/17860, WO 96/24609, WO 96/25426, WO 96/32110, WO 97/01338, WO 97/02284, WO 97/15190, WO 97/23499, WO 97/30708, WO 97/40024, WO 97/46577, WO 98/06740, WO 97/49404, WO 97/11693, WO 97/24135, WO 97/47299, WO 98/01422, WO 98/57932, WO 99/29664, WO 98/06741, WO 99/37668, WO 99/37611, WO 98/37075, WO 99/00371, WO 99/28297, WO 99/29670, WO 99/40072, WO 99/54313, WO 96/31504,

WO 00/01704, WO 00/08014, WO 00/35869, WO 00/42059, WO 00/61577, WO 00/61608, WO 00/61609, WO 01/87879, WO 02/14270 and WO 02/44145; and European Patent Applications 648 780, 468 231, 559 046, 641 779, 185 390, 526 877, 542 525, 195 212, 362 002, 364 344, 530 167, 293 881, 686 642, 669 317, 601 459 and 623 596.

In particular, international patent application WO 94/29336 discloses a group of compounds, including HOOC-CH_2-(*R*)Cgl-(*S*)Aze-Pab-H (in which Cgl represents cyclohexylglycine, Aze represents azetidine-2-carboxylic acid and Pab-H represents 4-aminomethyl-amidinobenzene), which is also known as melagatran (see Example 1 of WO 94/29336). International Patent Application WO 97/23499 discloses prodrugs of *inter alia* melagatran.

More recently, international patent application WO 02/44145 discloses α-hydroxy acid-based low molecular weight thrombin inhibitors and prodrugs thereof.

To the applicant's knowledge, none of the above-mentioned documents disclose or suggest the direct use a low molecular weight thrombin inhibitor or a prodrug thereof in cholesterol-lowering therapy and/or modifications of lipid (including triglyceride), lipoprotein, or apolipoprotein, profiles.

Disclosure of the Invention

We have found, surprisingly, that administration of a low molecular weight thrombin inhibitor may give rise to reduced levels of lipids, such as total cholesterol, LDLs (i.e. LDL-cholesterol) and triglycerides in the bloodstream, in addition to increasing HDL (i.e. HDL-cholesterol) levels.

According to a first aspect of the invention there is provided the use of a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for use in cholesterol-lowering therapy.

When employed in the context of the present invention and disclosure, the term "cholesterol-lowering therapy" includes any therapy that results in beneficial modifications of serum profiles of total cholesterol, lipids (including triglycerides), lipoproteins or apolipoproteins, and will thus be understood to encompass the terms "lipid-modifying therapy" and "lipid-(and triglyceride-) lowering therapy", as well as the treatment of hyperlipidaemias (i.e. the elevation of lipids in the bloodstream), including hypercholesterolaemia (high cholesterol levels in the blood; including primary and secondary (combined) hypercholesterolaemia), hyperlipoproteinemia (elevated plasma lipoproteins levels) and/or hypertriglyceridemia (high triglyceride levels in the blood). The term will thus be understood to include types I, II (IIa and IIb), III, IV and/or V hyperlipoproteinaemia, as well as secondary hypertriglyceridaemia and/or familial lecithin cholesterol acyltransferase deficiency, but in principle includes any treatment of a patient which results in a decrease in serum levels of cholesterol, LDLs, VLDLs, triglycerides and/or ApoB, and/or an increase in serum levels of HDLs and/or ApoA-I.

According to a second aspect of the invention there is provided a cholesterol-lowering therapy method, which method comprises the administration of a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, to a patient in need of such therapy.

For the avoidance of doubt, in the context of this disclosure, the terms "treatment", "therapy" and "therapy method" include the therapeutic and/or prophylactic treatment of patients in need of modifications of cholesterol, lipid (including triglyceride), lipoprotein and/or apolipoprotein profiles.

"Pharmaceutically acceptable derivatives" of thrombin inhibitors includes salts (e.g. pharmaceutically-acceptable non-toxic organic or inorganic acid addition salts) and solvates. It will be appreciated that the term further includes derivatives that have, or provide for, the same biological function and/or activity as any relevant inhibitor. Thus, for the purposes of this invention, the term also includes prodrugs of thrombin inhibitors.

The term "low molecular weight thrombin inhibitor" will be understood by those skilled in the art. The term may also be understood to include any composition of matter (e.g. chemical compound) which inhibits thrombin to an experimentally determinable degree in *in vivo* and/or in *in vitro* tests, and which possesses a molecular weight of below 2,000, preferably below 1,000.

Preferred low molecular weight thrombin inhibitors include low molecular weight peptide-based, amino acid-based, and/or peptide analogue-based, thrombin inhibitors.

The term "low molecular weight peptide-based, amino acid-based, and/or peptide analogue-based, thrombin inhibitors" will be well understood by one skilled in the art to include low molecular weight thrombin inhibitors with one to four peptide linkages, and includes those described in the review paper by Claesson in Blood Coagul. Fibrin. (1994) **5**, 411, as well as those disclosed in US Patent N° 4,346,078; International Patent Applications WO 93/11152,

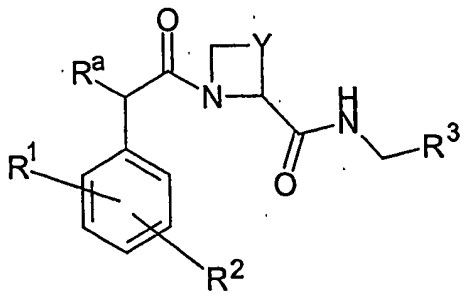
WO 93/18060, WO 93/05069, WO 94/20467, WO 94/29336, WO 95/35309, WO 95/23609, WO 96/03374, WO 96/06832, WO 96/06849, WO 96/17860, WO 96/24609, WO 96/25426, WO 96/32110, WO 97/01338, WO 97/02284, WO 97/15190, WO 97/30708, WO 97/40024, WO 97/46577, WO 98/06740, WO 97/49404, WO 97/11693, WO 97/24135, WO 97/47299, WO 98/01422, WO 98/57932, WO 99/29664, WO 98/06741, WO 99/37668, WO 99/37611, WO 98/37075, WO 99/00371, WO 99/28297, WO 99/29670, WO 99/40072, WO 99/54313, WO 96/31504, WO 00/01704, WO 00/08014, WO 00/35869, WO 00/42059, WO 00/61577, WO 00/61608, WO 00/61609, WO 01/87879, WO 02/14270 and WO 02/44145; and European Patent Applications 648 780, 468 231, 559 046, 641 779, 185 390, 526 877, 542 525, 195 212, 362 002, 364 344, 530 167, 293 881, 686 642, 669 317, 601 459 and 623 596, the specific and generic disclosures in all of which documents are hereby incorporated by reference.

Preferred low molecular weight peptide-based thrombin inhibitors include those described generically and specifically in international patent application WO 98/37075, including the compound that is the subject of Claim 8 of that application as published (1-methyl-2-[N-(4-amidinophenyl)aminomethyl]-benzimidazol-5-yl-carboxylic acid, N-(2-pyridyl)-N-(2-hydroxycarbonyl-ethyl)amide) and prodrugs thereof, and the compound that is the subject of Claim 10 of that application as published (1-methyl-2-[N-[4-(N-*n*-hexyloxycarbonylamidino)phenyl]aminomethyl]benzimidazol-5-yl-carboxylic acid, N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)amide).

Preferred low molecular weight peptide-based thrombin inhibitors also include HOOC-CH_2-(*R*)Cha-Pic-Nag-H (wherein Cha represents cyclohexylalanine, Pic represents (*S*)-pipecolinic acid and Nag represents noragmatine; known as inogatran; see International Patent Application WO

93/11152) and, especially, HOOC-CH_2-(*R*)Cgl-(*S*)Aze-Pab-H (known as melagatran; see above and International Patent Application WO 94/29336).

Further thrombin inhibitors include those of the formula I,



I

wherein

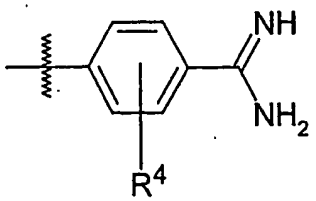
R^a represents -OH or -CH_2OH;

R^1 represents at least one optional halo substituent;

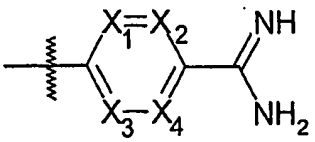
R^2 represents one or two C_{1-3} alkoxy substituents, the alkyl parts of which substituents are themselves substituted with one or more fluoro substituents (i.e. R^2 represents one or two fluoroalkoxy(C_{1-3}) groups);

Y represents -CH_2- or -$(CH_2)_2$-; and

R^3 represents a structural fragment of formula I(i) or I(ii):



I(i)



I(ii)

wherein

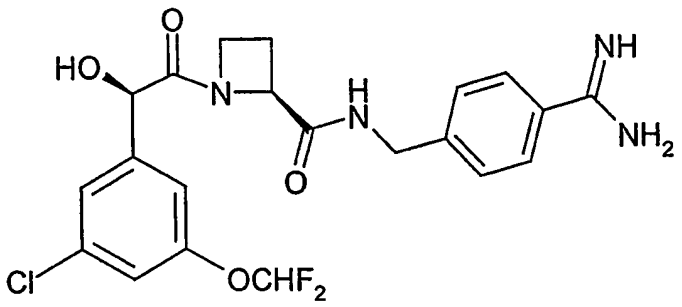
R^4 represents H or one or more fluoro substituents; and

one or two of X_1, X_2, X_3 and X_4 represent -N- and the others represent -CH-,

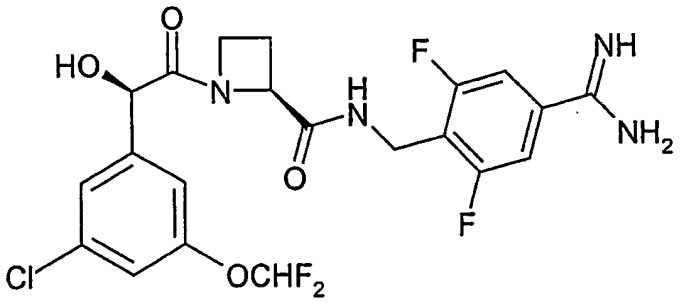
and pharmaceutically-acceptable derivatives thereof.

Preferred compounds of formula I include:

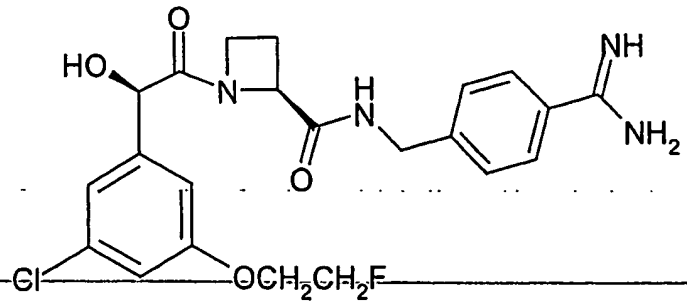
(a) Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab:



(b) Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(2,6-diF):



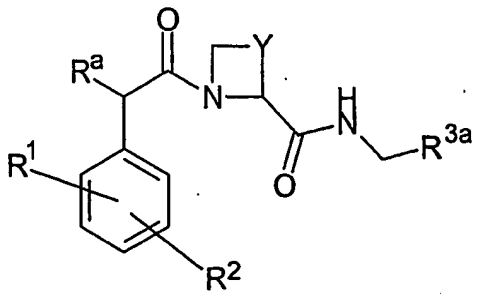
(c) Ph(3-Cl)(5-OCH_2CH_2F)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab:



The term "prodrug" of a low molecular weight thrombin inhibitor includes any compound that, following oral or parenteral administration, is metabolised *in vivo* to form a low molecular weight thrombin inhibitor (as defined herein), in an experimentally-detectable amount, and within a predetermined time (e.g. within a dosing interval of between 6 and 24 hours (i.e. once to four times daily)). For the avoidance of doubt, the term "parenteral" administration includes all forms of administration other than oral administration.

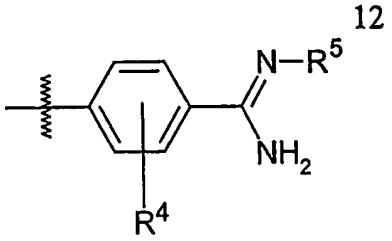
Prodrugs of the thrombin inhibitor melagatran that may be mentioned include those disclosed in international patent application WO 97/23499. Preferred prodrugs are those of the formula R^1O_2C-CH_2-(*R*)Cgl-(*S*)Aze-Pab-OH (see the list of abbreviations above or in WO 97/23499), wherein R^1 represents C_{1-10} alkyl or benzyl, such as linear or branched C_{1-6} alkyl (e.g. C_{1-4} alkyl, especially methyl, propyl and, particularly, ethyl) and the OH group replaces one of the amidino hydrogens in Pab.

Preferred prodrugs of compounds of formula I that may be mentioned include those of formula Ia,

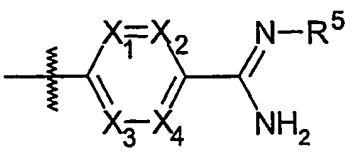


Ia

wherein R^{3a} represents a structural fragment of formula I(iii) or I(iv):



I(iii)



I(iv)

wherein R^5 represents OR^6 or $C(O)OR^7$;

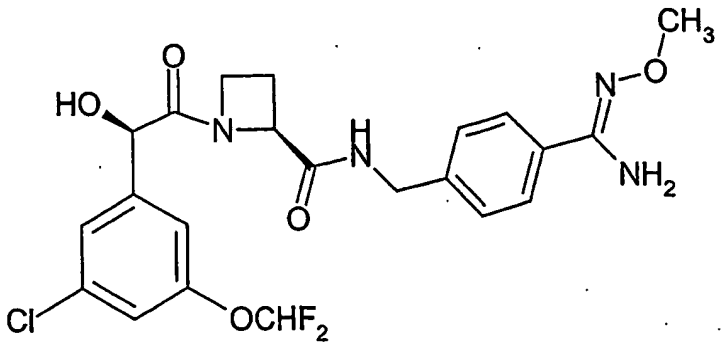
R^6 represents H, C_{1-10} alkyl, C_{1-3} alkylaryl or C_{1-3} alkyloxyaryl (the alkyl parts of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected from halo, phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents);

R^7 represents C_{1-10} alkyl (which latter group is optionally interrupted by one or more oxygen atoms), or C_{1-3} alkylaryl or C_{1-3} alkyloxyaryl (the alkyl parts of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected from halo, phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents); and

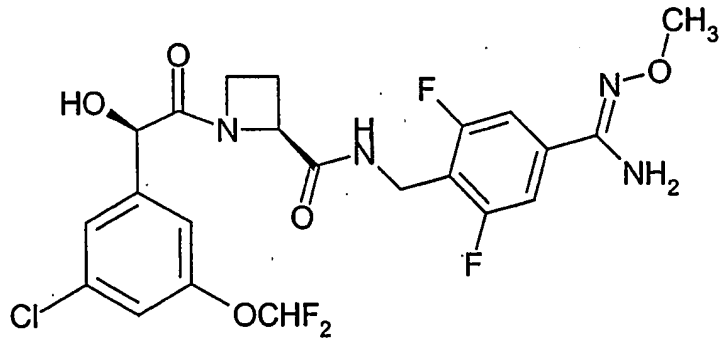
R^a, R^1, R^2, Y, R^4, X_1, X_2, X_3 and X_4 are as hereinbefore defined.

Preferred prodrugs of compounds of formula I are methoxyamidine prodrugs thereof. Hence preferred compounds of formula Ia include:

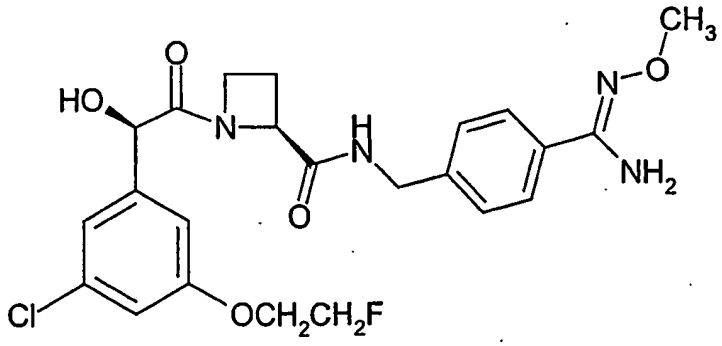
(i) Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(OMe):



(ii) Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(2,6-diF)(OMe):



(iii) Ph(3-Cl)(5-OCH_2CH_2F)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(OMe):



Compounds of formulae I and Ia may be made in accordance with techniques described in international patent application WO 02/44145.

In accordance with the invention, thrombin inhibitors and derivatives thereof may be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, topically, by any other parenteral route, or *via* inhalation, in the form of a pharmaceutical preparation comprising the thrombin inhibitor or prodrug in a pharmaceutically acceptable dosage form. Depending on the disorder, and the patient, to be treated, as well as the route of administration, the compositions may be administered at varying doses.

Preferred modes of delivery are systemic. For melagatran and derivatives thereof, preferred modes of administration are parenteral, more preferably intravenous, and especially subcutaneous. For prodrugs of melagatran and compounds of formula Ia, preferred modes of administration are oral.

In the therapeutic treatment of mammals, and especially humans, thrombin inhibitors, prodrugs of thrombin inhibitors, and derivatives of either will generally be administered as a pharmaceutical formulation in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, which may be selected with due regard to the intended route of administration and standard pharmaceutical practice.

Suitable formulations for use in administering thrombin inhibitors are known in the art, and include those known from US Patent N° 4,346,078; International Patent Applications WO 93/11152, WO 93/18060, WO 93/05069, WO 94/20467, WO 94/29336, WO 95/35309, WO 95/23609, WO 96/03374, WO 96/06832, WO 96/06849, WO 96/17860, WO 96/24609, WO 96/25426, WO 96/32110, WO 97/01338, WO 97/02284, WO 97/15190, WO 97/30708, WO 97/40024, WO 97/46577, WO 98/06740, WO 97/49404, WO 97/11693, WO 97/24135, WO 97/47299, WO 98/01422, WO 98/57932, WO

99/29664, WO 98/06741, WO 99/37668, WO 99/37611, WO 98/37075, WO 99/00371, WO 99/28297, WO 99/29670, WO 99/40072, WO 99/54313, WO 96/31504, WO 00/01704, WO 00/08014, WO 00/35869, WO 00/42059, WO 00/61577, WO 00/61608, WO 00/61609, WO 01/87879, WO 02/14270 and WO 02/44145; and European Patent Applications 648 780, 468 231, 559 046, 641 779, 185 390, 526 877, 542 525, 195 212, 362 002, 364 344, 530 167, 293 881, 686 642, 669 317, 601 459 and 623 596, the disclosures in all of which documents are hereby incorporated by reference.

Suitable formulations for use with melagatran, derivatives and prodrugs thereof are described in the literature, for example as described in *inter alia* international patent applications WO 94/29336, WO 96/14084, WO 96/16671, WO 97/23499, WO 97/39770, WO 97/45138, WO 98/16252, WO 99/27912, WO 99/27913, WO 00/12043 and WO 00/13671, the disclosures in which documents are hereby incorporated by reference. Otherwise, the preparation of suitable formulations may be achieved non-inventively by the skilled person using routine techniques.

The amounts of thrombin inhibitor or derivative in the formulation will depend on the severity of the condition, and on the patient, to be treated, as well as the compound(s) which is/are employed, but may be determined non-inventively by the skilled person.

Suitable doses of thrombin inhibitors and derivatives thereof in the therapeutic and/or prophylactic treatment of mammalian, especially human, patients may be determined routinely by the medical practitioner or other skilled person, and include the respective doses discussed in the relevant prior art documents that are mentioned hereinbefore, the relevant disclosures in which are hereby incorporated by reference.

In the case of melagatran, suitable doses of active compound, prodrugs and derivatives thereof, in the therapeutic and/or prophylactic treatment of mammalian, especially human, patients include those which give a mean plasma concentration of up to 5 μmol/L, for example in the range 0.001 to 5 μmol/L over the course of treatment of the relevant condition. Suitable doses may thus be in the range 0.1 mg once daily to 25 mg three times daily, and/or up to 100 mg infused parenterally over a 24 hour period, for melagatran, and in the range 0.1 mg once daily to 100 mg three times daily for prodrugs of melagatran (see also the specific doses mentioned hereinafter for the prodrug of melagatran, ximelagatran).

In the case of compounds of formulae I and Ia, suitable daily doses of the compounds of the invention in therapeutic treatment of humans are about 0.001-100 mg/kg body weight at peroral administration and 0.001-50 mg/kg body weight at parenteral administration.

In any event, the physician, or the skilled person, will be able to determine the actual dosage which will be most suitable for an individual patient, which is likely to vary with the severity of the condition that is to be treated, as well as the age, weight, sex and response of the particular patient to be treated. The above-mentioned dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Low molecular weight thrombin inhibitors may be employed in the method described herein by way of co-administration along with other cholesterol-lowering, or lipid lowering/modifying, drugs/therapies that are mentioned hereinbefore, such as the statins (HMG-CoA reductase inhibitors) and

particularly any one of those statins specifically mentioned hereinbefore, in combination therapy.

The method described herein may have the advantage that, in cholesterol-lowering therapy, it may be more convenient for the physician and/or patient than, be more efficacious than, be less toxic than, have a broader range of activity than, be more potent than, produce fewer side effects than, or that it may have other useful pharmacological properties over, similar methods (treatments) known in the prior art for use in such therapy.

The invention is illustrated, but in no way limited, by the following example, in which:

Figure 1 illustrates the difference in mean values (with 95% Confidence Intervals) of total cholesterol levels in serum as between patients receiving ximelagatran (36 mg bid) or warfarin (INR levels between 2 and 3) during the course of a clinical trial over a 21 month period.

Figure 2 illustrates the difference in mean values (with 95% Confidence Intervals) of levels of total triglycerides in serum as between patients receiving ximelagatran (36 mg bid) or warfarin (INR levels between 2 and 3) during the course of a clinical trial over a 21 month period.

Figure 3 illustrates the difference in mean values (with 95% Confidence Intervals) of LDL (i.e. LDL-cholesterol) levels in serum as between patients receiving ximelagatran (36 mg bid) or warfarin (INR levels between 2 and 3) during the course of a clinical trial over a 21 month period.

Figure 4 illustrates the difference in mean values (with 95% Confidence Intervals) of HDL (i.e. HDL-cholesterol) levels in serum as between patients receiving ximelagatran (36 mg bid) or warfarin (INR levels between 2 and 3) during the course of a clinical trial over a 21 month period.

Example

Lipid Measurements in Patients Undergoing Thrombin Inhibition Therapy in a Clinical Trial

A large-scale Phase III clinical trial was set up to establish the efficacy of the study compound EtO_2C-CH_2-(*R*)Cgl-(*S*)Aze-Pab-OH (ximelagatran; see Example 17 of international patent application WO 97/23499) in the prevention of stroke in patients with non-valvular atrial fibrillation, as compared to the current frontline treatment for this indication, warfarin.

Ximelagatran is a prodrug of the low molecular weight thrombin inhibitor, melagatran (see Example 1 of international patent application WO 94/29226).

The clinical trial protocol was similar to that described in international patent application WO 02/36157, with the following major differences:

(a) the study objective was to show that the efficacy of ximelagatran is non-inferior to that of dose-adjusted warfarin, aiming for an INR 2.0-3.0 (with INR measurements taken at least every 28 ± 3 days) in the prevention of all strokes (fatal and non-fatal) and systemic embolic events in patients with chronic non-valvular atrial fibrillation;

(b) the dosage of ximelagatran was fixed at 36 mg bid;

(c) in the exclusion criteria, subjects who had experienced stroke within the previous 30 days or transient ischaemic attack within the previous 3 days

were excluded (as opposed to 2 years in the study described in WO 02/36157);

(d) the duration of treatment was long term (between 12 and 26 months); and

(e) the total number of patients in the trial was 3407 (as opposed to 220 in the study described in WO 02/36157). The study was a multicentre, multinational, IVRS-randomised, open-label, parallel-group study carried out across approximately 300 centres in approximately 25 countries.

Over the first 21 months of the trial, blood samples were taken from all patients in a standard manner at the following intervals: beforehand, and at, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, and 21, months. These samples were routinely analysed for total cholesterol, LDL (i.e. LDL-cholesterol), HDL (i.e. HDL-cholesterol), and total triglycerides, content using standard techniques for the detection of these lipids in serum.

A comparison was made between patients on ximelagatran (n = 1704) and warfarin (n = 1703). When the raw data were analysed, an unexpected statistically-significant difference in favour of the ximelagatran group was observed. As of the second month of treatment, marked mean differences were observed for cholesterol, triglycerides and LDL serum concentrations (consistently significantly lower in the ximelagtran group over the entire 21 month period), and for the HDL serum concentration (consistently significantly higher in the ximelagtran group over the entire 21 month period), as illustrated in Figures 1 to 4, respectively.

These data clearly demonstrate the potential utility of melagatran and derivatives thereof (e.g. prodrugs, such as ximelagtran), as well as,

potentially, low molecular weight thrombin inhibitors and derivatives/prodrugs thereof, in cholesterol-lowering therapy.

Claims

1. The use of a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for use in cholesterol-lowering therapy.

2. The use of a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for the treatment of hypercholesterolaemia, hyperlipoproteinaemia and/or hypertriglyceridaemia.

3. The use as claimed in Claim 1 or Claim 2, wherein the therapy/treatment results in a decrease in serum levels of cholesterol, low-density lipoproteins, very low-density lipoproteins, triglycerides and/or apolipoprotein B; and/or an increase in serum levels of high-density lipoproteins and/or apolipoprotein A-I.

4. The use as claimed in any one of the preceding claims, wherein the thrombin inhibitor is melagatran.

5. The use as claimed in Claim 4, wherein the derivative of melagatran is a prodrug of melagatran.

6. The use as claimed in Claim 5, wherein the prodrug is of the formula

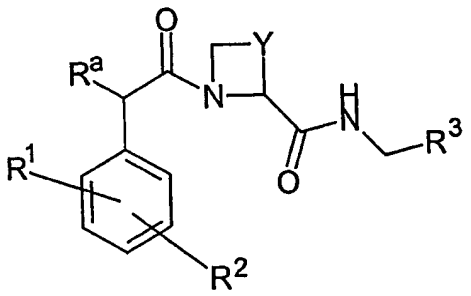
$$R^1O_2C\text{-}CH_2\text{-}(R)Cgl\text{-}(S)Aze\text{-}Pab\text{-}OH,$$

wherein R^1 represents linear or branched $C_{1\text{-}6}$ alkyl and the OH group replaces one of the amidino hydrogens in Pab.

7. The use as claimed in Claim 6, wherein R^1 represents methyl, ethyl or propyl.

8. The use as claimed in Claim 7, wherein R^1 represents ethyl.

9. The use as claimed in any one of Claims 1 to 3, wherein the thrombin inhibitor is of formula I,



I

wherein

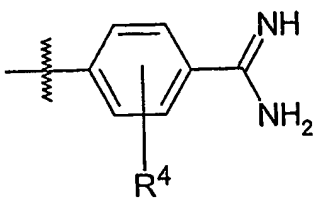
R^a represents -OH or $-CH_2OH$;

R^1 represents at least one optional halo substituent;

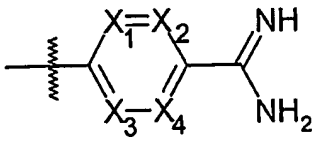
R^2 represents one or two C_{1-3} alkoxy substituents, the alkyl parts of which substituents are themselves substituted with one or more fluoro substituents;

Y represents $-CH_2-$ or $-(CH_2)_2-$; and

R^3 represents a structural fragment of formula I(i) or I(ii):



I(i)



I(ii)

wherein

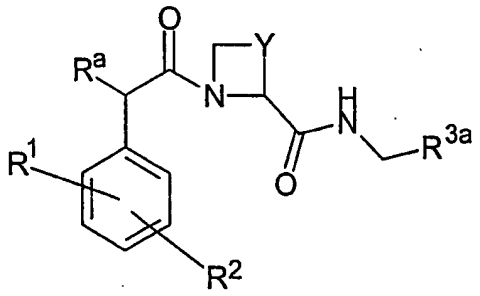
R^4 represents H or one or more fluoro substituents; and

one or two of X_1, X_2, X_3 and X_4 represent -N- and the others represent -CH-.

10. The use as claimed in Claim 9, wherein the thrombin inhibitor is:
Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab;
Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(2,6-diF); or
Ph(3-Cl)(5-OCH_2CH_2F)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab.

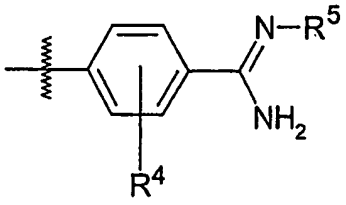
11. The use as claimed in Claim 9 or Claim 10, wherein the derivative of the thrombin inhibitor is a prodrug of that inhibitor.

12. The use as claimed in Claim 11, wherein the prodrug is of formula Ia,

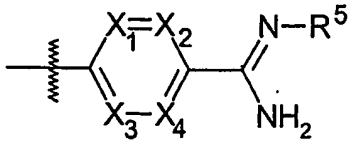


Ia

wherein R^{3a} represents a structural fragment of formula I(iii) or I(iv):



I(iii)



I(iv)

wherein R^5 represents OR^6 or $C(O)OR^7$;

R^6 represents H, C_{1-10} alkyl, C_{1-3} alkylaryl or C_{1-3} alkyloxyaryl (the alkyl parts of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected from halo, phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents);

R^7 represents C_{1-10} alkyl (which latter group is optionally interrupted by one or more oxygen atoms), or C_{1-3} alkylaryl or C_{1-3} alkyloxyaryl (the alkyl parts of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected from halo, phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents); and

R^a, R^1, R^2, Y, R^4, X_1, X_2, X_3 and X_4 are as defined in Claim 9.

13. The use as claimed in Claim 12, wherein the prodrug is:

Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(OMe);

Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(2,6-diF)(OMe); or

Ph(3-Cl)(5-OCH_2CH_2F)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(OMe).

14. A cholesterol-lowering therapy method, which method comprises the administration of a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, to a patient in need of such therapy.

15. A method of treatment of hypercholesterolaemia, hyperlipoproteinaemia and/or hypertriglyceridaemia, which method comprises the administration of a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, to a patient in need of such treatment.

16. The method as claimed in Claim 14 or Claim 15 wherein the therapy/treatment results in a decrease in serum levels of cholesterol, low-density lipoproteins, very low-density lipoproteins, triglycerides and/or apolipoprotein B; and/or an increase in serum levels of high-density lipoproteins and/or apolipoprotein A-I.

17. The method as claimed in any one of Claims 14 to 16, wherein the thrombin inhibitor is melagatran.

18. The method as claimed in Claim 17, wherein the derivative of melagatran is a prodrug of melagatran.

19. The method as claimed in Claim 18, wherein the prodrug is of the formula

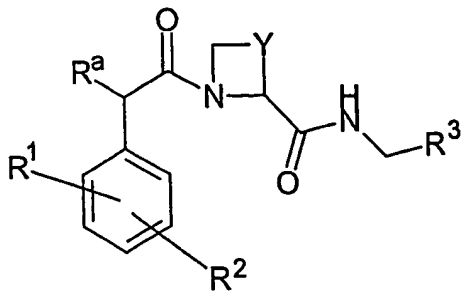
$$R^1O_2C\text{-}CH_2\text{-}(R)Cgl\text{-}(S)Aze\text{-}Pab\text{-}OH,$$

wherein R^1 represents linear or branched C_{1-6} alkyl and the OH group replaces one of the amidino hydrogens in Pab.

20. The method as claimed in Claim 19, wherein R^1 represents methyl, ethyl or propyl.

21. The method as claimed in Claim 20, wherein R^1 represents ethyl.

22. The method as claimed in any one of Claims 14 to 16, wherein the thrombin inhibitor is of formula I,



I

wherein

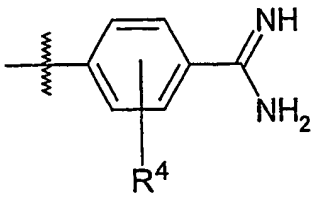
R^a represents -OH or $-CH_2OH$;

R^1 represents at least one optional halo substituent;

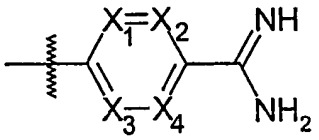
R^2 represents one or two C_{1-3} alkoxy substituents, the alkyl parts of which substituents are themselves substituted with one or more fluoro substituents;

Y represents $-CH_2-$ or $-(CH_2)_2-$; and

R^3 represents a structural fragment of formula I(i) or I(ii):



I(i)



I(ii)

wherein

R^4 represents H or one or more fluoro substituents; and

one or two of X_1, X_2, X_3 and X_4 represent -N- and the others represent -CH-.

23. The method as claimed in Claim 22, wherein the thrombin inhibitor is:

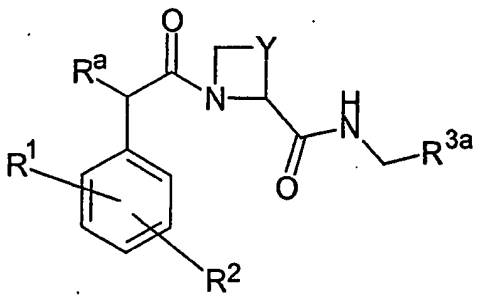
Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab;

Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(2,6-diF); or

Ph(3-Cl)(5-OCH_2CH_2F)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab.

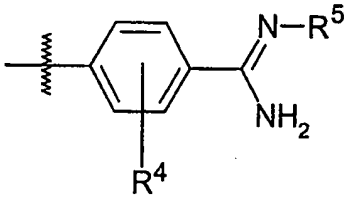
24. The method as claimed in Claim 22 or Claim 23, wherein the derivative of the thrombin inhibitor is a prodrug of that inhibitor.

25. The method as claimed in Claim 24, wherein the prodrug is of formula Ia,

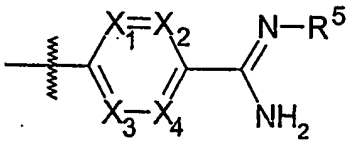


Ia

wherein R^{3a} represents a structural fragment of formula I(iii) or I(iv):



I(iii)



I(iv)

wherein R^5 represents OR^6 or $C(O)OR^7$;

R^6 represents H, C_{1-10} alkyl, C_{1-3} alkylaryl or C_{1-3} alkyloxyaryl (the alkyl parts of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected from halo, phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents);

R^7 represents C_{1-10} alkyl (which latter group is optionally interrupted by one or more oxygen atoms), or C_{1-3} alkylaryl or C_{1-3} alkyloxyaryl (the alkyl parts

of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected from halo, phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents); and

R^a, R^1, R^2, Y, R^4, X_1, X_2, X_3 and X_4 are as defined in Claim 22.

26. The method as claimed in Claim 25, wherein the prodrug is:

Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(OMe);

Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(2,6-diF)(OMe); or

Ph(3-Cl)(5-OCH_2CH_2F)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(OMe).

27. A pharmaceutical formulation for use in cholesterol-lowering therapy, which formulation comprises an effective amount of a low molecular weight thrombin inhibitor, or a pharmaceutically-acceptable derivative thereof.

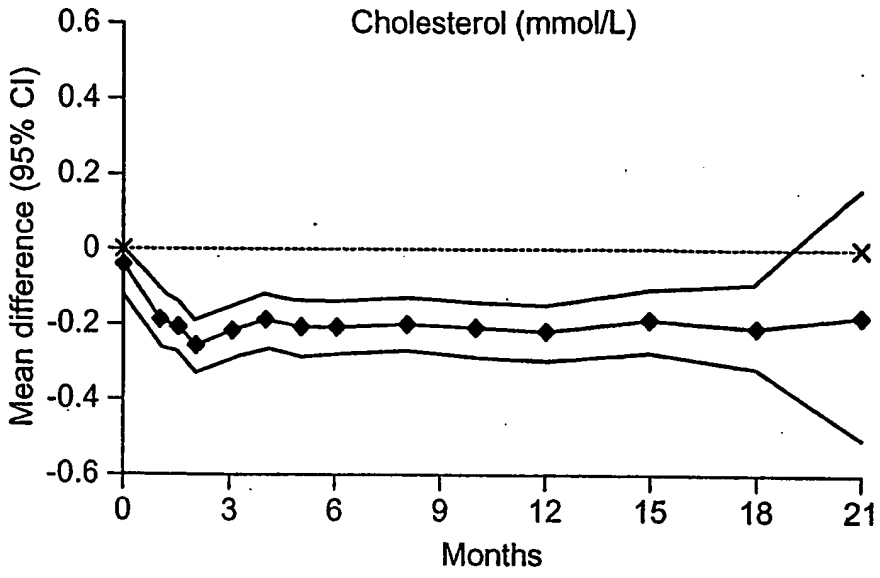
28. Use of a low molecular weight thrombin inhibitor, or a pharmaceutically-acceptable derivative thereof, in cholesterol-lowering therapy, by administering that inhibitor, or pharmaceutically-acceptable derivative, to a patient.

29. The use of a low molecular weight thrombin inhibitor, or a pharmaceutically-acceptable derivative thereof, in cholesterol-lowering therapy.

ABSTRACT

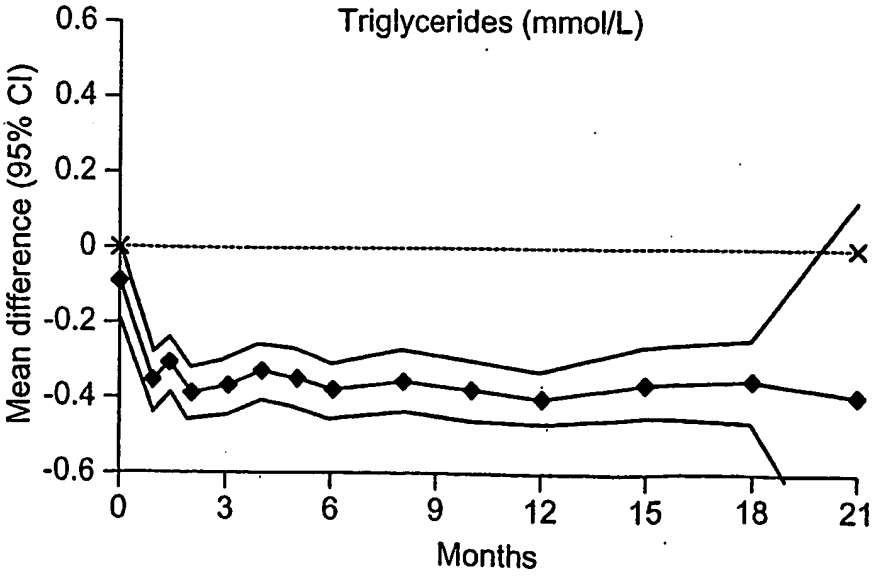
According to the invention there is provided the use of a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for use in cholesterol-lowering therapy and/or modification of lipid (triglyceride), lipoprotein, and apolipoprotein, profiles associated with an increased risk of cardiovascular complications.

Figure 1



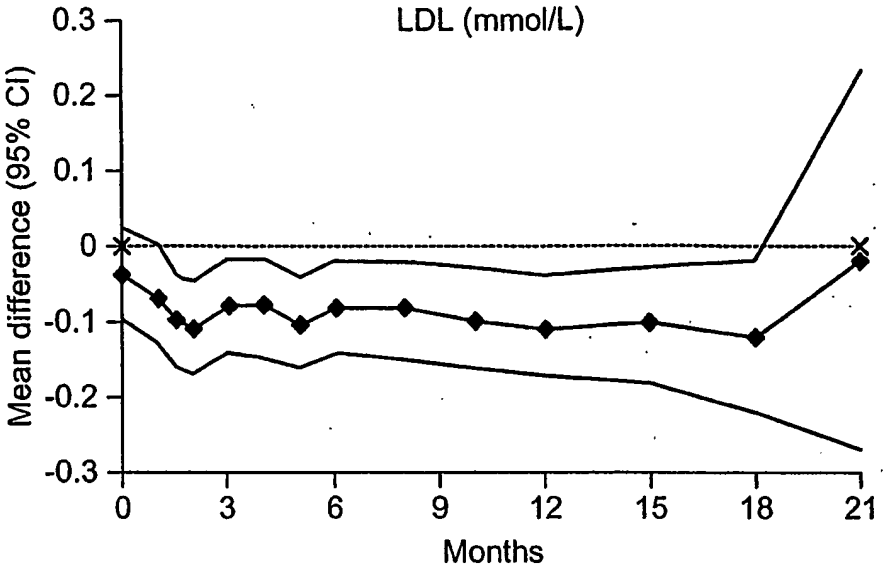
Mean at baseline: ximelagatran 5.27, warfarin 5.32

FIG. 1



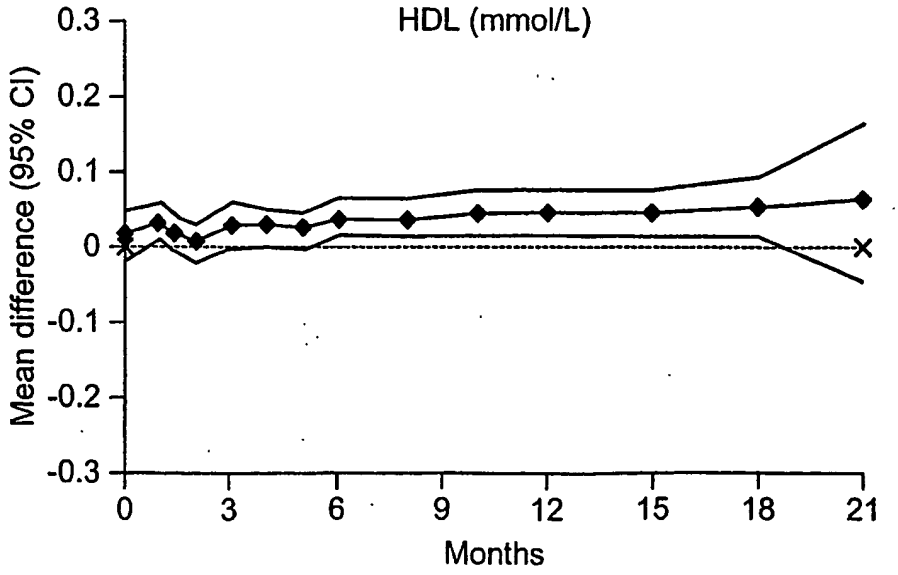
Mean at baseline: ximelagatran 1.86, warfarin 1.95

FIG. 2



Mean at baseline: ximelagatran 3.14, warfarin 3.18

FIG. 3



Mean at baseline: ximelagatran 1.31, warfarin 1.28

FIG. 4